

## Effects of acute aerobic exercise on brain-derived neurotrophic factor level in rheumatoid arthritis patients

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### ABSTRACT

**Objectives:** The study aimed to investigate the variation of brain-derived neurotrophic factor (BDNF) levels following acute exercise in patients with rheumatoid arthritis (RA).

**Patients and methods:** This cross-sectional study was conducted with 88 participants (25 males, 63 females; mean age: 45.1±8.3 years; range, 18 to 65 years) between July 2020 and May 2021. Of the participants, 44 were RA patients, and 44 were age- and sex-matched healthy controls. Aerobic exercise was utilized in all participants for a single session. Depression and anxiety levels were evaluated with the Beck Depression Inventory and Hospital Anxiety and Depression Scale. Blood samples were collected from all subjects before and immediately after the intervention.

**Results:** Serum BDNF levels (both baseline and after exercise) were similar in the RA and control groups. Although serum BDNF levels significantly decreased in both groups after aerobic exercise (Wilcoxon rank  $p<0.05$ ),  $\Delta$ BDNF levels were significantly higher in the RA group than in the control group ( $p=0.047$ ). Additionally,  $\Delta$ BDNF levels were significantly correlated with the Hospital Anxiety and Depression Scale scores in the RA group ( $p<0.05$ ) but not in the control group.

**Conclusion:** A single bout of exercise may effectively decrease serum BDNF levels in patients with RA and healthy subjects. The long-term effect of exercise on BDNF levels should be investigated in prospective studies.

**Keywords:** Brain-derived neurotrophic factor, rheumatoid arthritis, physical exercise.

Rheumatoid arthritis (RA) is a chronic, inflammatory, rheumatic disease in which genetic and environmental factors play a role.<sup>1</sup> Rheumatoid arthritis may progress with articular and nonarticular involvement. Extra-articular symptoms appear in patients with more severe disease, but they can rarely occur before the onset of arthritis.<sup>2</sup> There may be other symptoms caused by both the inflammation and the chronic

disease effect, as well as the symptoms associated with the disease, such as depression, fatigue, physical inactivity, and decreased quality of life.<sup>3</sup>

Depression prevalence is found to increase in RA patients compared to the healthy population, and it is correlated with pain, decreased quality of life, fatigue, and physical disability. Major depression risk was revealed as 16.8% among RA patients in a meta-analysis. Depression prevalence

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was found to be 38.8% when Patient Health Questionnaire was used as an assessment tool and between 14.8 and 48% when the Hospital Anxiety and Depression Scale (HADS) was used.<sup>4</sup> Pathophysiology of depression in RA patients is still unknown. In addition, proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, Interleukin (IL)-1 beta, and IL-6, were thought to play a role in depression. However, there are studies demonstrating the possible association between depression and brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor, insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) in the general population.<sup>5</sup>

Brain-derived neurotrophic factor (may promote healing and survival and exert protective effects on neurons in the central and peripheral nervous system.<sup>6</sup> Brain-derived neurotrophic factor is secreted not only from the brain but also from contracted muscles. Autocrine and paracrine effects were described for BDNF without participation of circulation. Besides the neural role, BDNF secretion was reported to be associated with inflammatory reactions. It was found that BDNF production increased in response to proinflammatory cytokines, such as IL-6 and TNF-alpha.<sup>7</sup> Grimsholm et al.<sup>8</sup> found that plasma BDNF levels were higher in RA patients compared to the healthy population. Although there are studies investigating BDNF levels before and after anti-TNF treatment in RA patients,<sup>8,9</sup> there is no study investigating the effect of exercise on BDNF levels in RA patients.

Exercise has been found to have positive effects on cognitive functions and mood changes by modulating BDNF levels in recent studies. Acute or chronic exercise programs were mostly found to increase BDNF levels in human and animal studies.<sup>10,11</sup> Brain-derived neurotrophic factor levels in other chronic diseases such as multiple sclerosis and Alzheimer's disease were found to increase following exercise.<sup>12,13</sup> In addition, to the best of our knowledge, there is no study investigating the effects of exercise on BDNF levels in RA patients in the literature. In this context, this study aimed to investigate the variation of BDNF levels following acute exercise and the correlation between BDNF levels and psychological symptoms.

## PATIENTS AND METHODS

This cross-sectional study was conducted with 88 participants (25 males, 63 females; mean age: 45.1±8.3 years; range, 18 to 65 years) at the Rheumatology Department of the Firat University between July 2020 and May 2021. Of the participants, 44 were RA patients, and 44 were age and sex matched healthy controls. Patients were diagnosed according to the American College of Rheumatology criteria.<sup>2</sup> Patients with regular exercise habits, malignancy, or a history of pregnancy and incorporation, patients who had changes to their medical treatment in the last three months, those diagnosed with fibromyalgia syndrome or osteoarthritis in the lower extremity, patients with cardiac symptoms according to New York Heart Association, those treated for depression or anxiety, and those with dysfunction that can prevent physical activity were excluded from the study. Healthy participants who did not have exercise habits were included in this study.

The information regarding the age, body mass index, smoking/alcohol habits, duration of the disease, vocation, and having another chronic disease of the patients were asked and recorded. Depression levels were evaluated with the Beck Depression Inventory (BDI) and HADS. Before and immediately after the exercise, blood samples were taken from all subjects and centrifuged. Obtained serums were stored at -80°C until analyzed by enzyme-linked immunosorbent assay (ELISA).

Turkish version of the BDI was used to determine the depression levels of subjects. It consists of 21 items regarding pessimism, guilt, sleep, appetite, and fatigue, and each item is scored between 0 and 3. Higher scores shows the severity of depression.<sup>14</sup> A BDI score ≥18 was considered as a cut-off value for depression.<sup>15</sup> No patient or healthy subject was on antidepressant drugs.

The HADS, developed by Zigmond and Snaith,<sup>16</sup> determines anxiety disorders and depression among patients in nonpsychiatric clinics. It consists of 14 items, and each item is scored from 0 to 3. Seven items are associated with anxiety, and seven are related to depression. The score that can be obtained as a result of

the scale ranges from 0 to 21. Bjelland et al.<sup>17</sup> identified a score of 8 as a cut-off point.

All participants performed aerobic exercise for a single session. The maximum heart rate was calculated for each subject (220 beats/min-age), and a heart rate monitor (Polar FT 100, China) was used to follow the subjects' heart rate during aerobic exercise. The aerobic exercise was performed on a treadmill and included 5 min of warm-up, 20 min of walking exercise reaching 60 to 80% of maximum heart rate, and 5 min of cool-down. The treadmill speed was increased and decreased gradually.

For BDNF analysis, we collected venous blood from each subject, and the samples were allowed to clot and then centrifuged at 4000 rpm for 5 min. Afterward, supernatant from the serum was inserted into the tube and stored at -80°C until they were assayed. The BDNF serum measurement was determined using a commercially available ELISA kit according to the manufacturer's instructions (Elabscience Human BDNF ELISA Kit, catalog no. E-EL-H0010).

## Statistical analysis

Statistical analyses were conducted using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The continuous data obtained in the study were presented as mean  $\pm$  standard deviation. The demographic and clinical characteristics of the groups were determined. The chi-square test was used for categorical data. The difference among groups was determined by the Mann-Whitney U test. Data from repeated measurements were analyzed with the Wilcoxon rank test. A *p* value of <0.05 was considered statistically significant.

## RESULTS

One patient could not complete aerobic exercise due to pain in lower extremity. Therefore, she was not included in the final analyses. No significant differences were observed either in baseline characteristics including age, sex, and body mass index between RA patients and the control. The differences in baseline and postexercise serum BDNF levels between RA

**Table 1.** The demographics, clinical and laboratory data in the study groups

Characteristics or measurement	RA group (n=44)			HC group (n=44)			<i>p</i>
	n	%	Mean $\pm$ SD	n	%	Mean $\pm$ SD	
Age (year)			46.8 $\pm$ 10.3			43.4 $\pm$ 6.4	0.828 <sup>a</sup>
Smoking							0.622 <sup>b</sup>
Yes	12	27.3		10	22.7		
No	32	72.7		34	77.3		
BMI (kg/m <sup>2</sup> )			26.8 $\pm$ 4.6			25.6 $\pm$ 2.4	0.317 <sup>a</sup>
Sex	32	72.7		31	70.5		0.813 <sup>b</sup>
Females							
Disease duration (year)			8.6 $\pm$ 7.3			-	-
HADS depression			10.2 $\pm$ 3.9			2.2 $\pm$ 2.1	<0.001 <sup>a</sup>
HADS anxiety			10.4 $\pm$ 4.1			2.4 $\pm$ 2.1	<0.001 <sup>a</sup>
BDI			17.9 $\pm$ 8.1			3.7 $\pm$ 4.1	<0.001 <sup>a</sup>
BDNF (baseline) (pg/mL)			798.9 $\pm$ 381.1			688.7 $\pm$ 469.9	0.069 <sup>c</sup>
BDNF (post-exercise) (pg/mL)			469.5 $\pm$ 193.5			509.9 $\pm$ 380.4	0.593 <sup>c</sup>
$\Delta$ BDNF (pg/mL)			329.5 $\pm$ 258.4			211.1 ( $\pm$ 302.6)	0.047 <sup>c</sup>
BDNF increased	2	4.5		13	30.2		0.002 <sup>b</sup>

RA: Rheumatoid arthritis; HC: Healthy controls; SD: Standard deviation; BMI: Body mass index, BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; BDNF: Brain-derived neurotrophic factor; a: Student's t-test; b: Chi-square test; c: Mann-Whitney U test.

**Table 2.** Comparison of  $\Delta$ BDNF levels according to the use of MTX, GCs, and anti-TNF drugs

Patients according to treated drugs	Patients		$\Delta$ BDNF levels	
	n	%	Mean $\pm$ SD	p
<b>MTX</b>				
User	18	40.9	261.97 $\pm$ 166.62	0.316
Non-user	26	59.1	376.18 $\pm$ 300.74	
<b>GC</b>				
User	19	43.1	444.03 $\pm$ 285.51	0.008
Non-user	25	56.9	242.39 $\pm$ 200.57	
<b>Anti-TNF</b>				
User	5	11.3	92.02 $\pm$ 112.06	0.013
Non-user	39	88.7	359.90 $\pm$ 256.67	

BDNF: Brain-derived neurotrophic factor; MTX: Methotrexate; GC: Glucocorticoid.

patients and the control were also insignificant ( $p>0.05$ ). However, significant differences were found in BDI, HADS depression, and HADS anxiety scores between the groups ( $p<0.001$ ; Table 1).

Serum BDNF levels significantly decreased after exercise in both RA and control groups (Wilcoxon rank  $p<0.05$ ; Figure 1). However, serum BDNF levels increased in 30.2% of the healthy subjects and 4.5% of the RA patients ( $p=0.002$ ). Between-group analyses showed that  $\Delta$ BDNF levels were significantly higher in the RA group than in the control group (Table 1).

Eighteen (40.9%) patients used methotrexate, 19 (43.1%) patients used a glucocorticoid (GC), and five (11.3%) patients used anti-TNF drugs. Significant differences were found in  $\Delta$ BDNF between users and nonusers of a GC or an anti-TNF ( $p<0.05$ ; Table 2).

Hospital Anxiety and Depression Scale anxiety scores were significantly correlated with  $\Delta$ BDNF levels in the RA group ( $p<0.05$ ) but not in the control group (Table 3). It was observed that individuals with increased BDNF levels after exercise in the control group had lower HADS depression and anxiety scores

**Table 3.** Significant correlations among measurements in the study groups

	RA group (n=44)		HC group (n=44)	
	r	p	r	p
BDI-HADS depression	<b>0.726</b>	<b>&lt;0.001</b>	<b>0.942</b>	<b>&lt;0.001</b>
BDI-HADS anxiety	<b>0.738</b>	<b>&lt;0.001</b>	<b>0.911</b>	<b>&lt;0.001</b>
HADS depression- $\Delta$ BDNF	0.257	0.093	0.211	0.175
HADS anxiety- $\Delta$ BDNF	<b>0.347</b>	<b>0.021</b>	0.126	0.421
BDNF (baseline)-BDNF (post-exercise)	<b>0.787</b>	<b>&lt;0.001</b>	<b>0.771</b>	<b>&lt;0.001</b>
BDNF (baseline)- $\Delta$ BDNF	<b>0.887</b>	<b>&lt;0.001</b>	<b>0.743</b>	<b>&lt;0.001</b>
BDNF (post-exercise)- $\Delta$ BDNF	<b>0.413</b>	<b>0.005</b>	0.146	0.351

RA: Rheumatoid arthritis; HC: Healthy controls; BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; BDNF: Brain-derived neurotrophic factor.

**Table 4.** Differences between increased and decreased BDNF levels in the control group

Characteristics or measurement	BDNF increased (n=13)	BDNF decreased (n=31)	p
	Mean±SD	Mean±SD	
Age (year)	44.8±6.8	43.0±6.3	0.523
BMI (kg/m <sup>2</sup> )	25.4±1.9	25.8±2.5	0.731
HADS depression	1.15±1.6	2.67±2.2	0.023
HADS anxiety	1.46±1.4	2.8±2.2	0.069
BDI	1.38±2.7	4.73±4.3	0.005
BDNF (baseline) (pg/mL)	374.7±306.7	824.7±466.5	0.001
BDNF (post-exercise) (pg/mL)	477.7±289.6	477.3±334.5	0.692

BDNF: Brain-derived neurotrophic factor; SD: Standard deviation; BMI: Body mass index; HADS: Hospital Anxiety and Depression Scale; BDI: Beck Depression inventory.

than individuals with decreased BDNF levels (Table 4). There was a significant correlation between basal BDNF levels and  $\Delta$ BDNF levels in both groups (Figure 2).

## DISCUSSION

A single bout of exercise may be effective on serum BDNF levels in patients with RA and healthy subjects. However, psychological comorbidities may affect the amelioration of BDNF levels in RA.

In this study, serum BDNF levels were found to be higher in RA patients than those of healthy controls at baseline, which is consistent with previous studies investigating BDNF levels in RA patients before and after anti-TNF treatment.<sup>8,9</sup> Kerschensteiner et al.<sup>18</sup> concluded that BDNF was involved in inflammatory reactions. Additionally, its level was reported to increase in response to proinflammatory cytokines.<sup>19</sup> It was found that IL-6 and TNF-alpha led to BDNF secretion by human peripheral blood monocytes.<sup>7</sup> Furthermore, BDNF is locally produced in the synovial tissue and can be detected in the inflammatory synovium of RA patients.<sup>20</sup> Therefore, a reason for high BDNF levels may be the inflammatory reactions in RA patients. Similarly, it was found that BDNF levels were higher in systemic lupus erythematosus (SLE) and primary Sjögren's syndrome patients compared to healthy controls.<sup>21,22</sup> Brain-derived neurotrophic factor levels were high in active SLE patients compared to inactive patients independent

of neuropsychiatric symptoms.<sup>22</sup> These findings may show that inflammation is a factor influencing BDNF levels. The second reason for this finding may stem from the role of BDNF as a pain modulator in the peripheral and central nervous system. Bringing BDNF to dorsal root ganglia was found to influence mechanical allodynia in normal rats, similar to allodynia produced by sciatic nerve transection.<sup>23</sup> Suppression of BDNF may inhibit central pain sensitization. Brain-derived neurotrophic factor is known to affect neuroplasticity, neuronal repair, learning, and memory. Chronic pain may be a consequence of neuroplastic changes in the central nervous system originating from peripheral nociceptive input. Permanent expression of the neurotrophin may play an important role in the development of latent stages of chronic pain.<sup>24</sup> These mechanisms may be interpreted as a reason for high levels of BDNF in diseases such as RA, FMS and SLE, in which chronic pain and central sensitization occur.

Exercise is known to be effective in depression, anxiety, and cognitive functions, possibly via BDNF regulated mechanism.<sup>25</sup> An upregulation of BDNF levels after acute and chronic exercise was found in many studies in patients with Alzheimer's disease, multiple sclerosis, and young and older healthy population.<sup>12,26-29</sup> Aerobic exercises were employed in some studies similar to our study,<sup>12,26,27</sup> while another study examined a combined exercise program including aerobic exercise and pilates training in patients with multiple sclerosis.<sup>29</sup> In this study, we found a

reduction in BDNF levels after acute exercise in RA patients and healthy controls and a significant difference in  $\Delta$ BDNF between the groups. This is the first study investigating the effects of acute exercise on BDNF levels in RA patients. This finding is contrary to those in the literature. This contrast may stem from inflammatory reactions or chronic pain. The endogenous opioid system acutely activates with exercise, which has clear antinociceptive effects with less effectiveness under chronic pain situations.<sup>30</sup> One speculative conclusion may be that the reduction of BDNF may be an indirect reason for pain relief. The possible importance of BDNF in pain relief and its association with exercise should be investigated further. Studies investigating high-intensity exercises were mostly concluded with an upregulation in BDNF.<sup>31,32</sup> No significant difference was found in studies evaluating strength exercise.<sup>33,34</sup>

Exercise has anti-inflammatory effects via anti-inflammatory cytokines. However, anti-inflammatory effects of acute exercise are controversial.<sup>35</sup> We did not investigate anti-inflammatory mediators. Therefore, it is not possible to explain the decrease in BDNF levels with the anti-inflammatory effects of exercise. Further studies should investigate the association of BDNF levels with inflammatory biomarkers after exercise intervention. Grimsholm et al.<sup>8</sup> observed a downregulation in BDNF levels after anti-TNF treatment in RA patients but no correlation with inflammatory parameters. Researchers concluded that this finding may be due to the pain-mediating effects of BDNF. Pedard et al.<sup>36</sup> investigated BDNF in adjuvant-induced arthritis in rats and reported no relationship with the arthritis score or proinflammatory cytokine levels.

A significant difference in  $\Delta$ BDNF levels was found between users and nonusers of anti-TNF treatment and GCs in this study. A reduction was observed in anti-TNF users, while an increment was observed in GC users. Adachi et al.<sup>37</sup> concluded that GC stimulates BDNF vesicle transport. Additionally, downregulation of BDNF levels after anti-TNF treatment was reported in the previous studies, which supports our results. The reason for the reduction was not established, but researchers suggested that the pain-mediating effect of BDNF may cause the finding.<sup>8,9</sup> Depression and anxiety are one of the most common symptoms in

patients with RA.<sup>38</sup> In this study, depression and anxiety levels were found to be higher in patients with RA than those of healthy controls. This finding is supported by previous studies. It was determined in a seven-year follow-up study that depression levels increased more in RA patients than the healthy population.<sup>38</sup> In a meta-analysis investigating 13,189 patients with RA, 38.8% of patients were reported to have depression, which was five times more likely compared to healthy individuals.<sup>4</sup> Pathogenesis of depression and anxiety is not clearly known. However, there are some hypotheses, such as lesions in the central nervous system, disease-related symptoms, or chronicity of the disease.<sup>38</sup> One of the hypotheses is the involvement of brain BDNF modulation as a mechanism by which peripheral inflammation may induce a depression-like phenotype.<sup>36</sup> Patients with depression were reported to have low levels of BDNF.<sup>39</sup> However, depression, anxiety, and BDNF levels were higher in RA patients compared to healthy controls at baseline in this study. This finding may point to inflammation and pain sensitization, as mentioned above.

Although depression and anxiety levels were higher in patients, a significant correlation was found only between  $\Delta$ BDNF and anxiety in our study. Stress causes a reduction in neurotrophin activity, which decreases neuronal proliferation and plasticity, possibly resulting in depression over time. Studies suggest that peripheral BDNF is a biomarker of depression.<sup>39,40</sup> However, we could not find a significant relationship between psychological assessments and the BDNF level at baseline in the patients and the control. One speculative suggestion may be that high levels of BDNF may cause inflammation and pain-mediating effects at baseline. However, different results may be obtained by increasing the number of participants.

The limitations of this study are its low sample size and not including inflammatory markers in the evaluation. Further studies should investigate the relationship between BDNF and inflammatory parameters before and after exercise. Other limitations may be related to exercise frequency. More detailed research may be obtained with a longstanding and planned exercise program for RA patients.

In conclusion, we found a down-regulation of serum BDNF levels in RA patients, which is the

major point of this study. Additionally, BDNF levels were higher in RA patients compared to healthy controls at baseline. This finding may be explained by the inflammation- and pain-mediating effects of BDNF. Our study is significant in that it is the first study investigating the effects of acute exercise on BDNF levels in patients with RA. Further studies are required to investigate the potential effects of exercise sessions and long-term exercise on BDNF levels.

**Ethics Committee Approval:** The study protocol was approved by the Firat University Clinical Research Ethics Committee (date: 14.11.2019, no: 04). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each participants.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Study conception and design, draft manuscript preparation and literature review: S.B.Y.; Data collection: S.B.Y., Z.E., G.D., S.S.K.; Analysis and interpretation of results: S.B.Y., S.S.K.; Critical review: S.B.Y., Z.E., S.S.K.; All authors reviewed the results and approved the final version of the manuscript.

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